(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 February 2002 (21.02.2002)

PCT

(10) International Publication Number
WO 02/14311 A2

(51) International Patent Classification[7]: C07D 417/00

(21) International Application Number: PCT/US01/25472

(22) International Filing Date: 15 August 2001 (15.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/225,793	15 August 2000 (15.08.2000)	US
Not furnished	14 August 2001 (14.08.2001)	US

(71) Applicant: **AMGEN INC.** [US/US]; One Amgen Center Drive, Thousand Oaks, CA 91320-1799 (US).

(72) Inventors: **SANTORA, Vincent**; 2623 Miller Place, Thousand Oaks, CA 91362 (US). **ASKEW, Benny**; 515 Havenside Avenue, Newbury Park, CA 91320 (US). **GHOSE, Arup**; 4023 Corte Cancion, Thousand Oaks, CA 91360 (US). **HAGUE, Andrew**; 488 Yorba Linda, Camarillo, CA 93012 (US). **KIM, Tae, Seong**; 1550 Dover Avenue, Thousand Oaks, CA 91360 (US). **LABER, Ellen**; 2589 Clearview Avenue, Ventura, CA 91362 (US). **LI, Aiwen**; Suite F, 587 North Ventu Park Road, P.O. Box 725, Newbury Park, CA 91320 (US). **LIAN, Brian**; 1322 Fenbrook Lane, Bloomington, IN 47401 (US). **LIU, Gang**; 491 Pesaro Street, Oak Park, CA 91377 (US). **NORMAN, Mark, Henry**; 130 Venus Street, Thousand Oaks, CA 91360 (US). **SMITH, Leon**; 33 Julie Court, Sommerset, NJ 08873 (US). **TASKER, Andrew**; 561 Granite Hills Street, Simi Valley, CA 93065 (US). **TEGLEY, Christopher**; 478 Thunderhead Street, Thousand Oaks, CA 91360 (US). **YANG, Kevin**; 8871 Camino Real Avenue, San Gabriel, CA 91775 (US).

(74) Agents: **ODRE, Steven, M.** et al.; Amgen Inc., One Amgen Center Drive, M/S 27-4-A, Thousand Oaks, CA 91320-1799 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

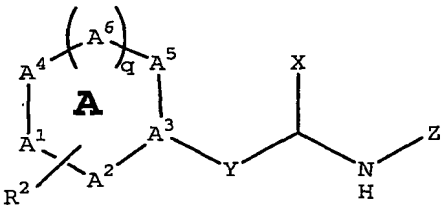
WO 02/14311 A2

(54) Title: UREA COMPOUNDS AND METHODS OF USES

(57) Abstract: Selected novel urea compounds are effective for prophylaxis and treatment of diseases, such as cell proliferation or apoptosis mediated diseases. The invention encompasses novel compounds, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compositions and methods for prophylaxis and treatment of diseases and other maladies or conditions involving stoke, cancer and the like. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

WHAT IS CLAIMED IS:

1. A compound of formula I



I

wherein each of A^1-A^6 is selected from CH_2, CH, C, O, S, NH and N; wherein A^1-A^6 together form a ring A selected from

additionally substituted or unsubstituted 5- or 6-membered heterocyclyl,

additionally substituted or unsubstituted 5- or 6-membered heteroaryl fused with a phenyl group,

additionally substituted or unsubstituted 5- or 6-membered cycloalkenyl, and

additionally substituted or unsubstituted phenyl,

wherein the ring A is additionally substituted with one or more substituents independently selected from halo, $-OR^3$, $-SR^3$, $-CO_2R^3$, $-CO_2NR^3R^3$, $-COR^3$, $-NR^3R^3$, $-SO_2NR^3R^3$, $-NR^3C(O)OR^3$, $-NR^3C(O)R^3$, cycloalkyl, optionally substituted phenylalkylenyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted heteroarylalkylenyl, optionally substituted phenyl, lower alkyl, cyano, lower hydroxyalkyl, nitro, lower alkenyl, lower alkynyl and lower haloalkyl;

wherein X and Z taken together form a nitrogen containing ring selected from

unsubstituted 5-6 membered heterocyclyl,

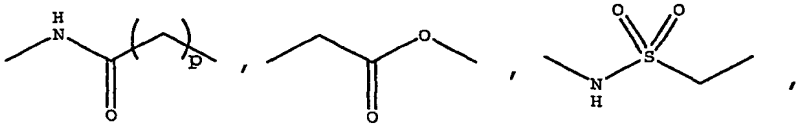
unsubstituted 5-6 membered heterocyclyl fused with a phenyl group,

5-6 membered heterocyclyl substituted with one or more substituents independently selected from R^1, and

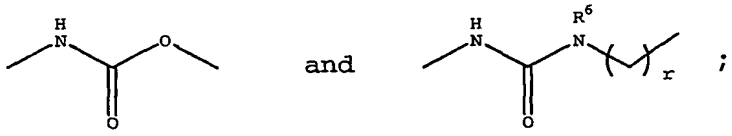
5-6 membered nitrogen-containing heterocyclyl, fused with a phenyl group, substituted with one or more substituents independently selected from R^1;

wherein R^1 is independently selected from H, halo, $-OR^3$, $-SR^3$, $-CO_2R^3$, $-CO_2NR^3R^3$, $-COR^3$, $-CONR^3R^3$, $-NR^3R^3$, $-C(S)NR^3R^3$, $-SO_2NR^3R^3$, $-NR^3C(O)OR^3$, $-NR^3C(O)R^3$, cycloalkyl, optionally substituted phenylalkylenyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted 4-10 membered heterocyclylalkyl, optionally substituted phenyl, optionally substituted phenoxy, lower alkyl, lower cyano, lower alkenyl, lower alkynyl and lower haloalkyl;

wherein Y is selected from, in either orientation,



and



;

wherein R^2 is selected from

lower alkylaminoalkynyl,

cycloalkenyl-C_{2-3}-alkynyl,

cycloalkyl-C_{2-3}-alkynyl,

phenyl-C_{2-3}-alkynyl,

5-6 membered heterocyclyl-C_{2-3}-alkynyl,
substituted or unsubstituted cycloalkenyl,
substituted or unsubstituted phenyl,
substituted or unsubstituted 5-6 membered heterocyclyl, and
substituted or unsubstituted 5-6 membered heterocyclyl bridged with a phenyl group;
wherein substituted R^2 is substituted with one or more substituents independently selected from halo, $-OR^3$, $-SR^3$, $-CO_2R^3$, $-CO_2NR^3R^3$, $-COR^3$, $-NR^3R^3$, $-C(O)NR^3R^3$, $-SO_2NR^3R^3$, $-NR^3C(O)OR^3$, $-NHC(O)R^3$, $-SO_2NHC(O)R^3$, $-C(S)NR^3R^3$, nitro, cycloalkyl, optionally substituted phenylalkylenyl, optionally substituted 4-7 membered heterocyclyl, optionally substituted heterocyclylalkylenyl, optionally substituted phenyl, optionally substituted phenoxyalkylenyl, optionally substituted heterocyclyloxyalkyl, lower alkyl, cyano, lower hydroxyalkyl, lower alkoxyalkyl, lower azidoalkyl, lower aminoalkyl, lower (hydroxyalkyl)aminoalkyl, lower alkylaminoalkyl, lower alkylaminoalkoxy, lower aminoalkoxyalkyl, lower (alkylaminoalkyl)amino lower ((alkylamino)alkylamino)alkyl, lower alkylaminoalkylaminocarbonyl, lower cyanoalkyl, lower alkenyl, lower alkynyl and lower haloalkyl;

wherein R^3 is selected from H, lower alkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted heterocyclyl,

optionally substituted heterocyclylalkyl, C_3-C_6 cycloalkyl, and lower haloalkyl;

wherein R^6 is selected from H, alkyl, 5-6 membered heterocyclylalkylenyl and alkylamino;

wherein p is 1 or 2;

wherein q is 0 or 1; and

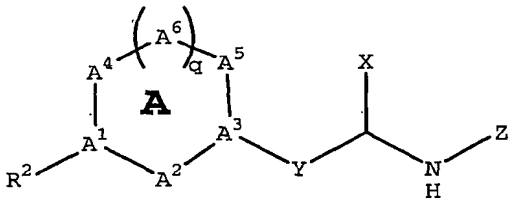
wherein r is 0-3;

and pharmaceutically acceptable salts thereof;

provided A is not thiazol-2-yl when Y is ureido; further provided A is not phenyl when R^2 is pyridyl or pyrimidyl when Y is ureido and when X and Z taken together form 1-methylindolyl; further provided A is not 1-phenylpyrazol-4-yl when Y is ureido when X and Z taken together form pyrazolyl and when R^2 is pyrrol-1-yl; further provided A is not 5-methylpyrazol-3-yl when Y is ureido when X and Z taken together form pyrazolyl and when R^2 is phenyl; further provided A is not thiazolyl or dihydrothiazolyl when R^2 is indolyl when Y is ureido and when X and Z taken together form thiazolyl or dihydrothiazolyl; further provided A is not pyrazolyl or dihydropyrazolyl when R^2 is 2-furyl when Y is ureido and when X and Z taken together form thiazolyl or dihydrothiazolyl when R^1 is isopropyl; further provided A is not oxadiazolyl or dihydrooxadiazolyl when R^2 is phenyl when Y is ureido and when X and Z taken together form thiazolyl or dihydrothiazolyl when R^1 is isopropyl; provided A is not thiazolyl when R^2 is 3-pyridyl when Y is ureido and when X and Z taken together form 2-(3-pyridyl)thiazol-4-yl; and further provided

A is not thien-3-yl when Y is ureido when X and Z taken together form thienyl and when R^2 is pyrrol-1-yl.

2. Compound of Claim 1 and pharmaceutically acceptable salts thereof, of formula Ia

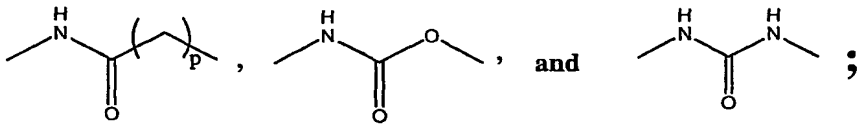


Ia.

3. Compound of Claim 2, and pharmaceutically acceptable salts thereof, wherein A is selected from 5- or 6- membered heterocyclyl.

4. Compound of Claim 3, and pharmaceutically acceptable salts thereof, wherein A is selected from 5- or 6- membered heteroaryl.

5. Compound of Claim 4, and pharmaceutically acceptable salts thereof, wherein A is selected from thiazolyl, oxazolyl, imidazolyl, pyrrolyl, pyrazolyl, isoxazolyl, triazolyl and isothiazolyl; wherein Y, in either orientation is selected from



wherein p is 1-2;